Coronary Microvascular Dysfunction: CMVD

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Introduction

- Also known as *Cardiac Syndrome X* or *CPNCA(Chest Pain with Normal Coronary Arteries)*
- Patients present with chest pain
- Investigations such as ECG, cardiac PET, cardiac MRI, myocardial scintigraphy are suggestive of ischemia.
- However, coronary angiograms are found to be normal.

Cardiac Syndrome X- Definition

Table 2. Definition of Cardiac Syndrome X (Adapted With Permission From Lanza[3])

Typical stable angina, exclusively or predominantly induced by effort
Findings compatible with myocardial ischemia/CMVD on diagnostic investigation*
Normal (or near normal†) coronary arteries on angiography
Absence of any other specific cardiac disease (eg, variant angina, cardiomyopathy, valvular disease)

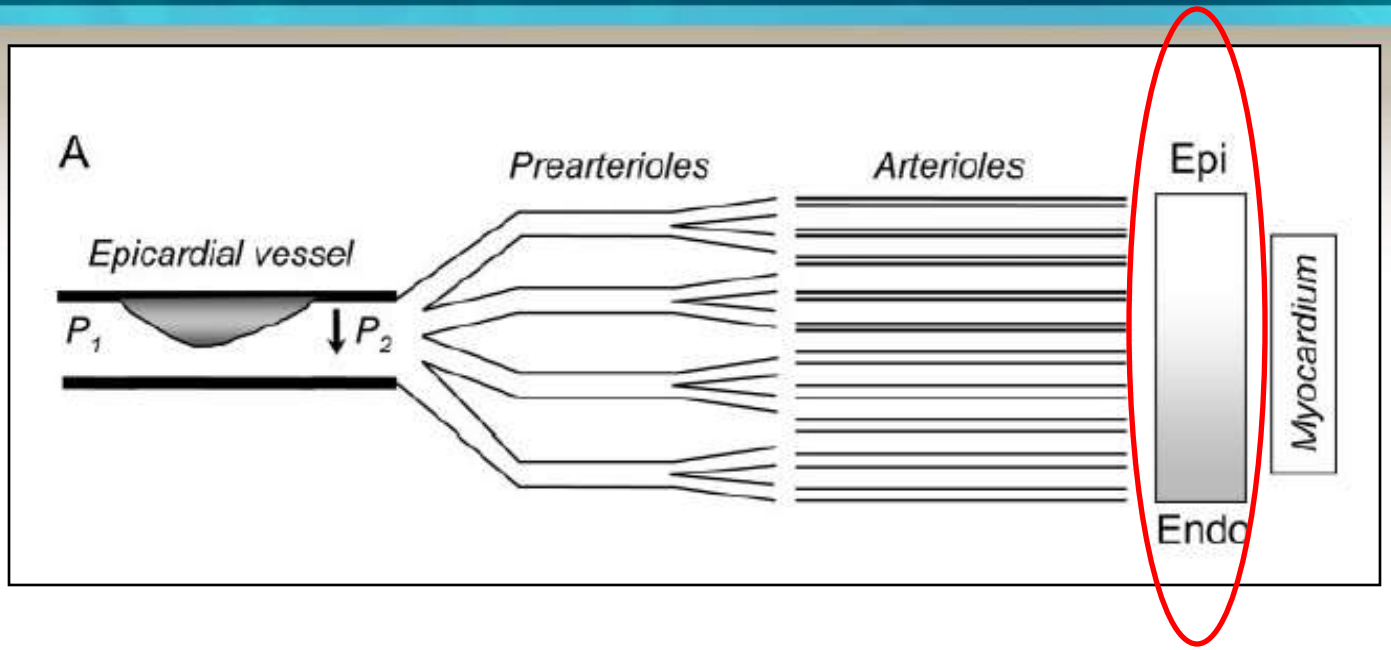
Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart*. 2007;93:159–166.

Classification of CMVD

Type of CMVD	Definition
Type 1	Primary i.e. in the absence of any structural heart disease
Type 2	In the presence of cardiomyopathies
Type 3	In the presence of obstructive CAD
Type 4	After coronary interventions
Type 5	After cardiac transplantations

Herrmann J. Coronary microvascular dysfunction in the clinical setting: from mystery to reality. European Heart Journal (2012) 33, 2771–2781

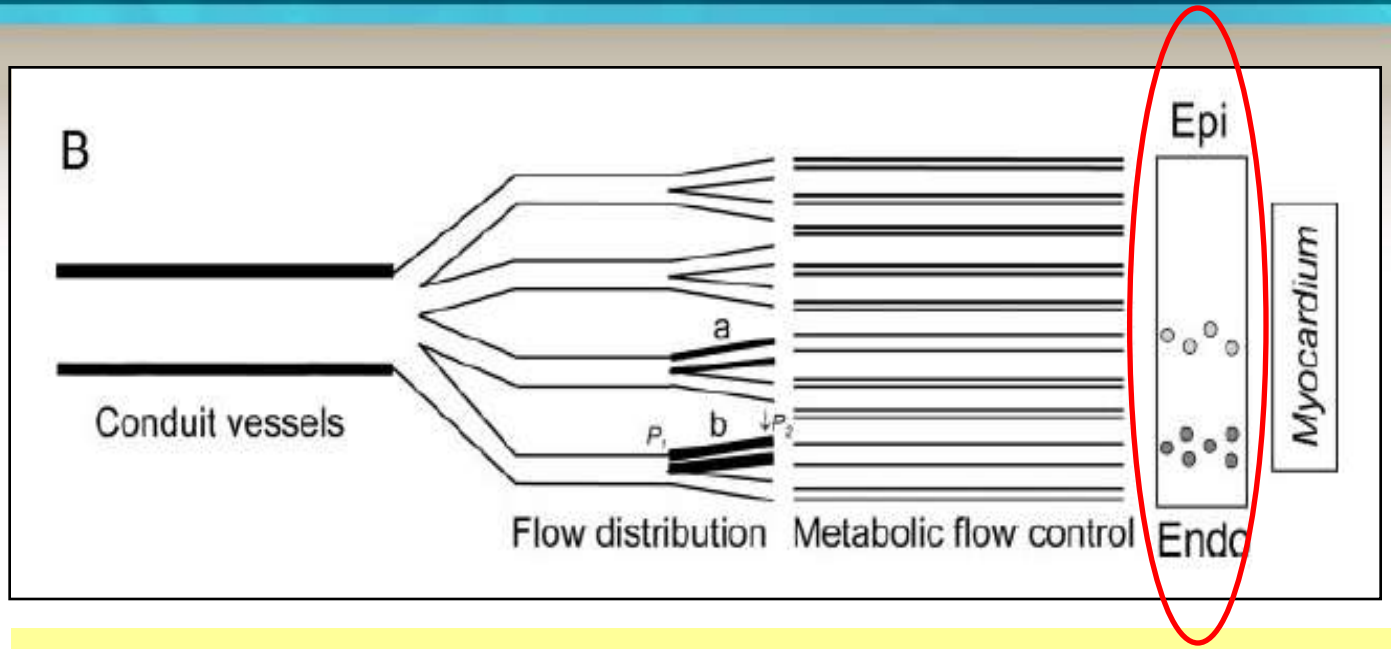
Pathogenesis



Epicardial Obstructive CAD

Myocardial ischemia diffusely involves the whole myocardial (usually subendocardial) territory supplied by the vessel (gray area), thus resulting in **regional contractile dysfunction**.

Pathogenesis



Coronary Microvascular Dysfunction

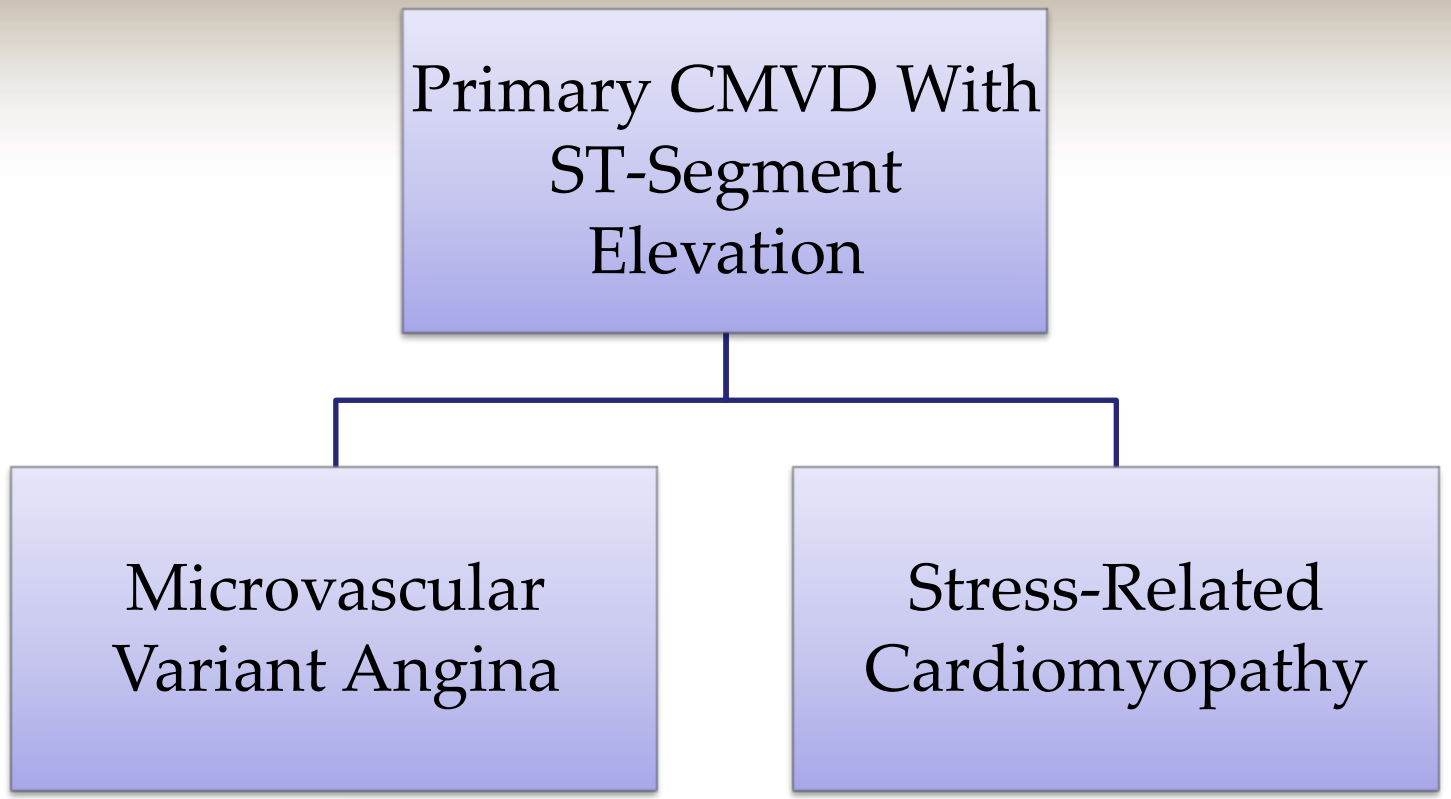
Myocardial ischemia is localized only in small myocardial areas, and patchily diffused (small circles); this **may not result in detectable contractile abnormalities** because of the presence of normal contractile myocardial cells in the same territory.

Abnormal Cardiac Pain Perception: The Sensitive Heart

- Some people are more sensitive to usual stimuli and hence perceive sensations differently
- Pain can be induced in such patients by by plain saline injections in coronaries, LV pacing, and by drugs like dipyridamole/adenosine
- These patients also show exagerrated pain responses in the esophagus during endoscopy
- Frequently associated with anxiety and panic disorders

Cannon O. Microvascular Angina and the Continuing Dilemma of Chest Pain with Normal Coronary Angiograms. J Am Coll Cardiol. 2009 September 1; 54(10): 877–885

Primary CMVD With ST-Segment Elevation



Microvascular "Variant Angina"

- Mohri et al, in patients with angina attacks at rest reported transient transmural myocardial ischemia, as indicated by ST-elevation, during spontaneous or provoked angina in the presence of normal coronary arteries.

- Intracoronary acetylcholine reproduced angina and ST-segment changes in the absence of epicardial spasm, thus suggesting diffuse coronary microvascular spasm.

- In these patients, Rho-kinase inhibitor like nicorandil/fasudil was effective, suggesting that enhanced rho-kinase activity, may be involved as a pathogenetic mechanism.

- CCBs are a possible alternative treatment.

Stress-Related Cardiomyopathy

- Also referred to as apical ballooning syndrome or Takotsubo disease
- Patients are usually postmenopausal women and usually present with symptoms and signs compatible with ACS
- Angiography shows normal coronary arteries and 2D echo shows LV apical and midventricular akinesia
- Despite this , only minor elevations of troponins and creatine kinase–MB occur
- Patient recovery in 1 to 3 months

Diagnosis

Diagnosis of MVD requires the exclusion of epicardial abnormalities by coronary angiography

In suspected cases, attempts should be made to obtain objective evidence of CMVD and possibly, of myocardial ischemia

Clinical Assessment

- Chest pain persists for several minutes after effort is interrupted and/or shows poor or slow response to nitroglycerin

- Induction of angina and ST segment depression, but not left ventricular contractile abnormalities, during an echocardiographic dipyridamole or dobutamine stress test

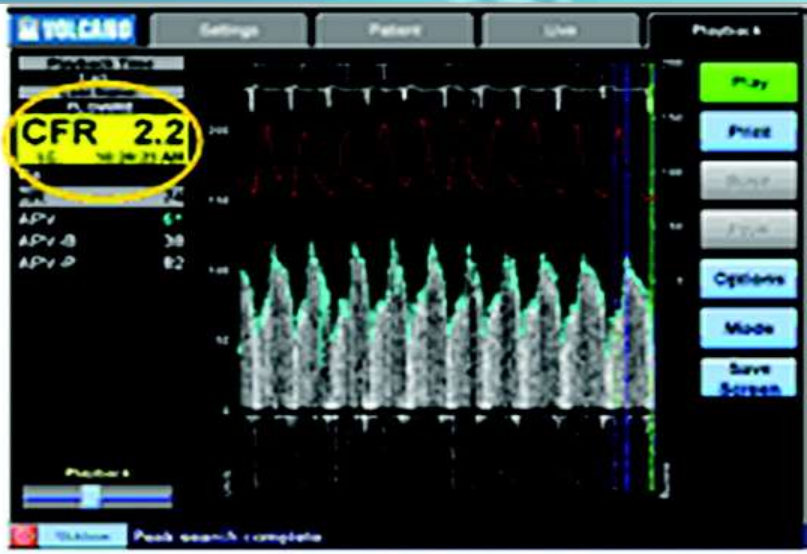
- Earlier appearance of ECG abnormalities and/or angina during an exercise test performed after sublingual nitrate administration.

Investigations

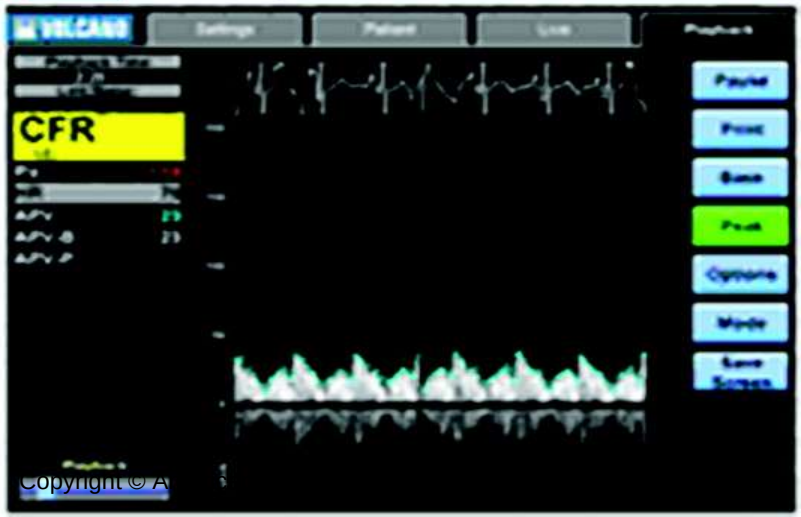
- Tests to identify CMVD should explore both the vasodilator and vasoconstrictor activity of coronary microcirculation.
- In patients with stable CMVD, vasodilator tests are the first choice
- When they are normal or inconclusive, response to vasoconstrictor stimuli should be assessed.

Intracoronary Doppler blood flow velocity waveforms in response to intracoronary adenosine and acetylcholine

$$\text{Coronary Flow Reserve (CFR)} = \left(\frac{\text{Peak Average Peak Velocity (PAPV)}}{\text{Baseline Average Peak Velocity (BAPV)}} \right)$$

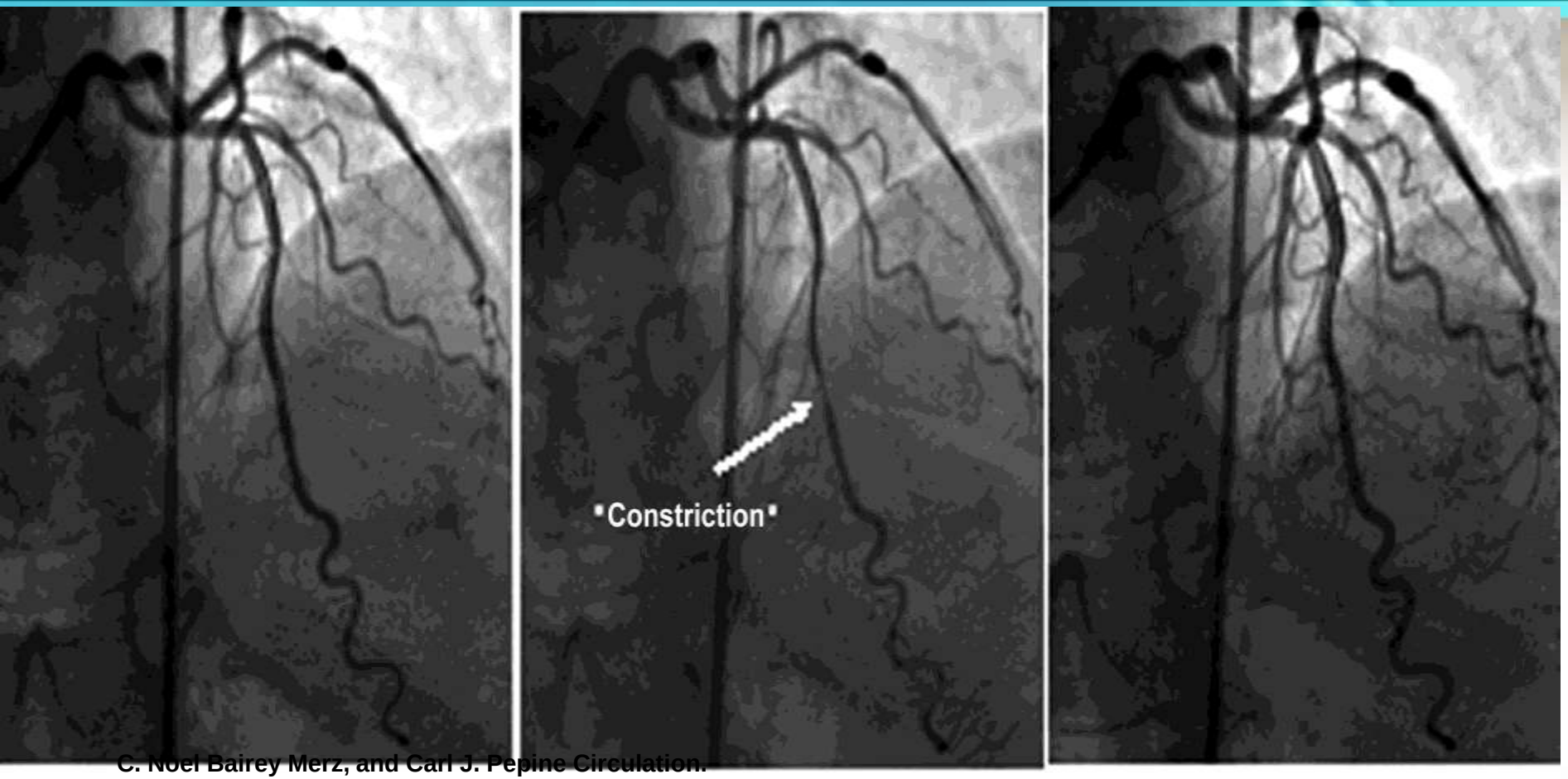


$$\text{Coronary Blood Flow Reserve (CBF)} = \left(\frac{\text{Peak } 3.1487\text{x (coronary artery diameter in mm/2) 2 x (average peak velocity/2)]}}{\text{Baseline } 3.1487\text{x (coronary artery diameter in mm/2) 2 x (average peak velocity/2)]}} \right)$$



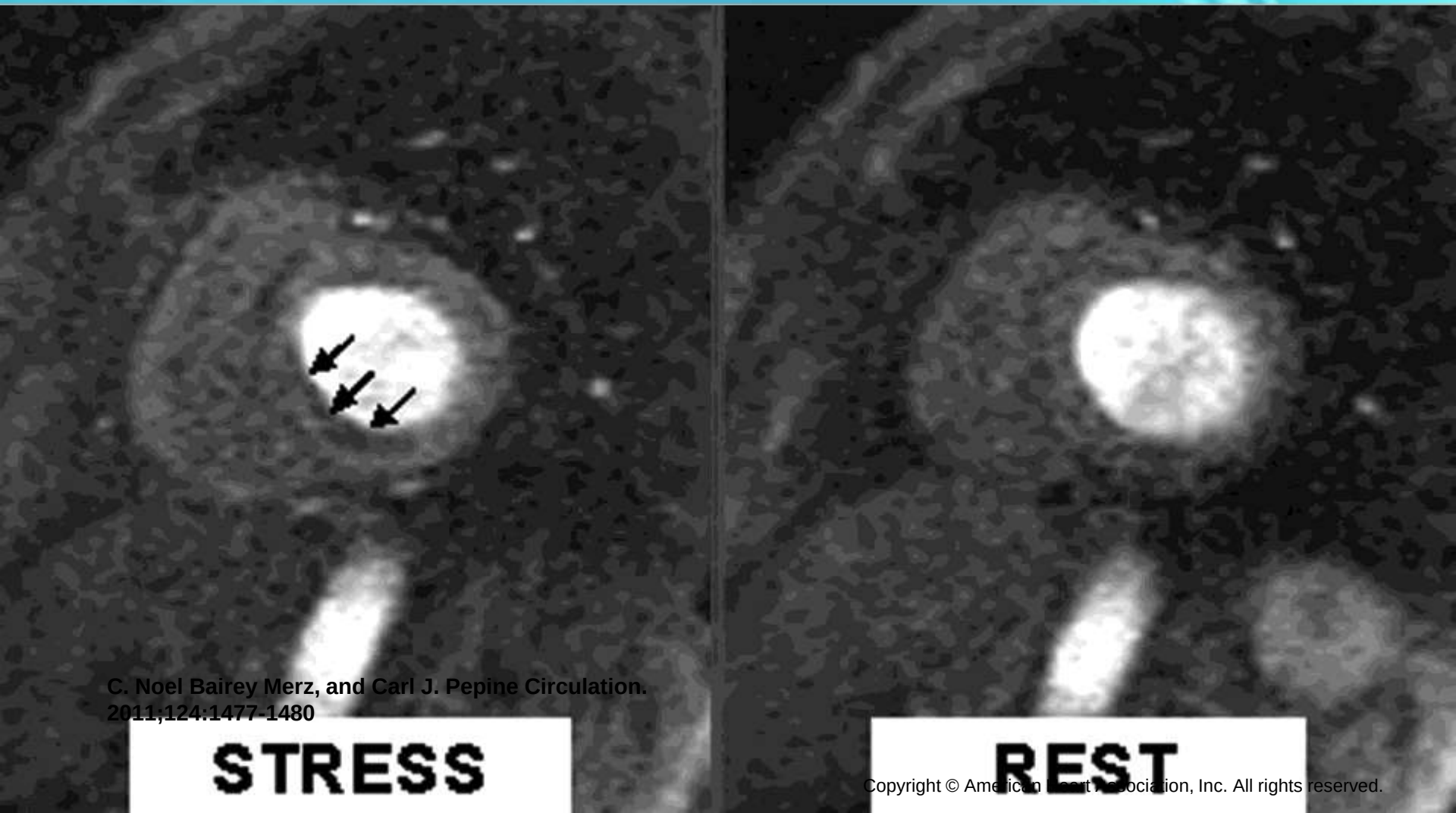
Cr. Noel Barrey Merz, and Carl J. Pepine Circulation. 2011;124:1477-1480

Intracoronary acetylcholine (ACH) demonstrating constriction of the coronary arteries (arrow) and intracoronary



C. Noel Bairey Merz, and Carl J. Pepine Circulation. 2011;124:1477-1480

Adenosine stress perfusion base-ventricle cardiac magnetic resonance imaging (left) and rest perfusion base-ventricle cardiac magnetic resonance imaging (right).



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Transthoracic echocardiographic Doppler recording

- Can be used as a first routine method to identify CMVD in patients with normal coronary arteries
- Ratio between diastolic CBF(coronary blood flow) velocity at peak vasodilation and CBF velocity at rest is assessed
- **A ratio 2.0 in response to adenosine (or dipyridamole) strongly suggests CMVD**

Cardiac Stress Probes

Imaging

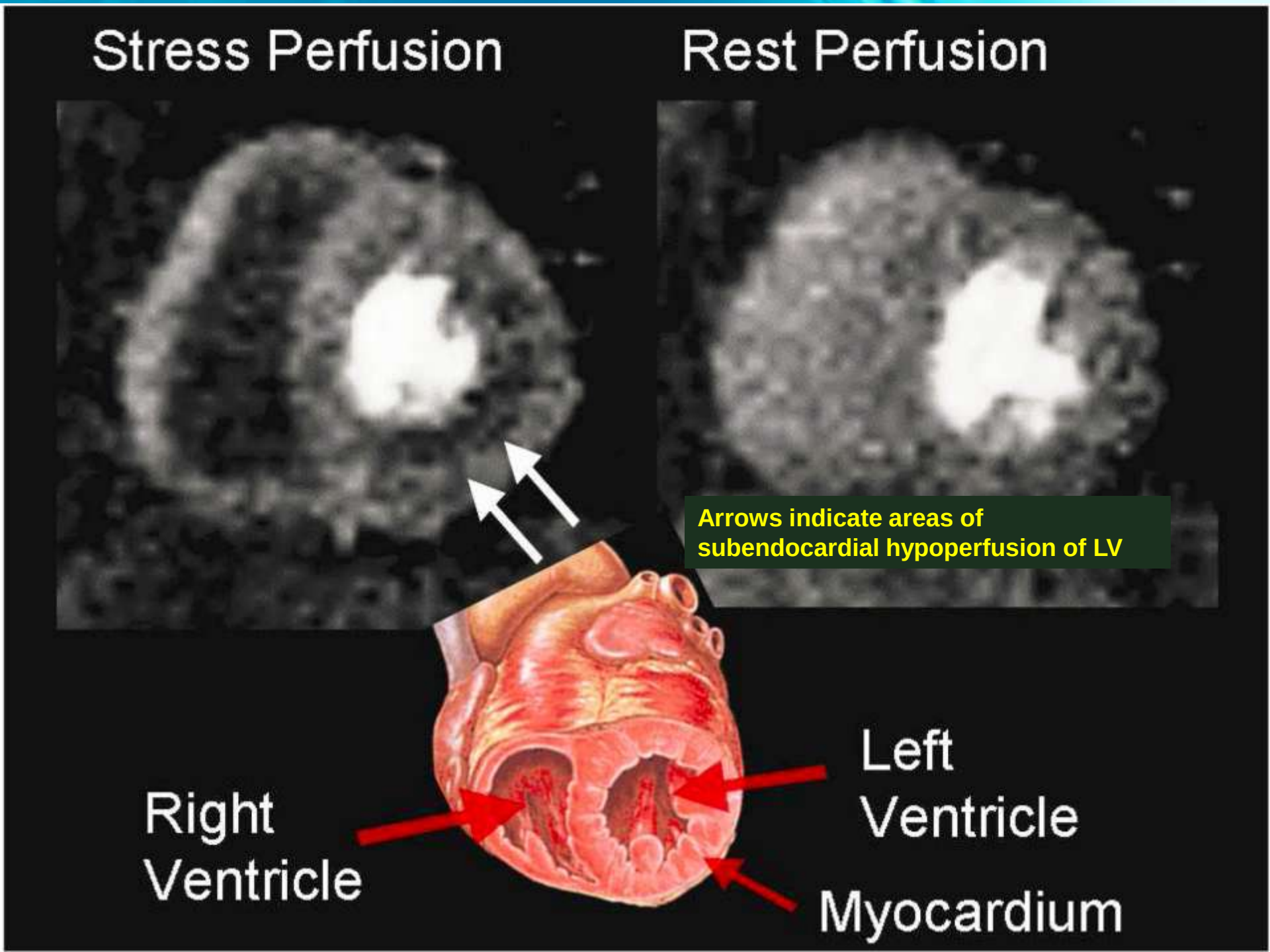
- Contrast stress echocardiography is a promising method to detect CMVD in different myocardial territories and may be used when TTE-DR is negative or inconclusive

- CMR imaging, with pharmacological stress tests and with gadolinium as a flow tracer, is perhaps the most promising method for noninvasive assessment

Imaging

- Myocardial perfusion imaging by scintigraphic stress test (SPECT, PET) is the most reliable tool available to diagnose myocardial perfusion and CMVD. But it is expensive and not easily available for routine use

- CMR spectroscopy can detect ischemic abnormalities of phosphorus metabolism under stress tests; however, this technique is expensive, has scarce availability, and can only explore the anterior wall of the heart.


Stress Perfusion
Rest Perfusion
Arrows indicate areas of subendocardial hypoperfusion of LV
Right Ventricle
Left Ventricle
Myocardium

Treatment

Initial Management

- Lifestyle Modification: Smoking cessation & weight loss
- Exercise Training: Helps with adrenergic modulation
- Statins and ACE inhibitors: In hypertensives, as these help in improving endothelial function

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Medical Management

- CCBs: Not very effective
- Beta blockers: Improve symptoms
- Sublingual /oral nitrates: Improve symptoms to a certain extent
- Ranolazine: Improves myocardial perfusion, angina status and exercise stress test results compared to ivabradine
- Nicorandil and Fasudil have also been tried with inconsistent results
- In hypertensive patients combinations of ACE-Inhibitors and thiazides have proved to be potentially effective

Alternative Management for Women

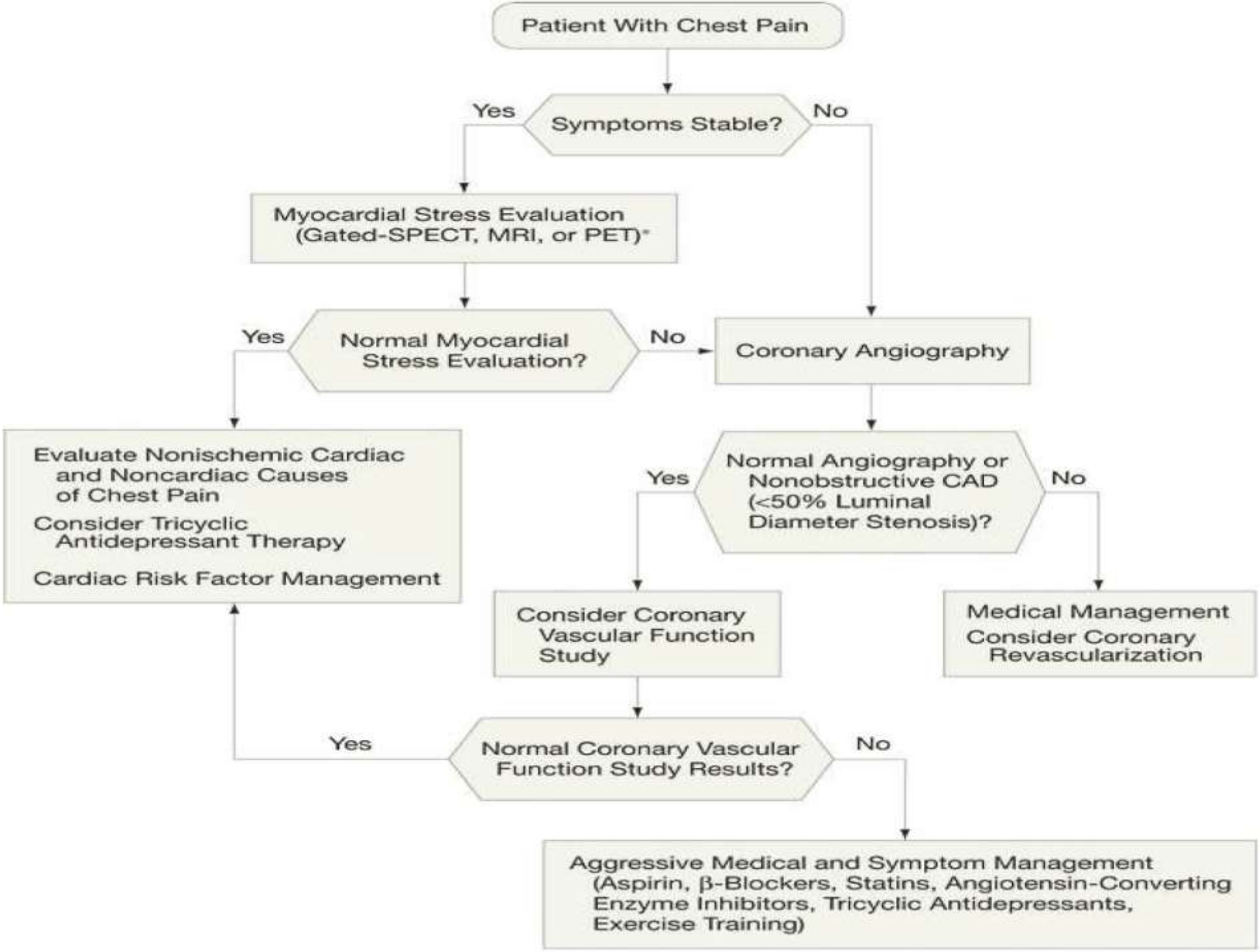
- Imipramine: Helps improve abnormal cardiac pain perception possibly through anticholinergic and alpha agonistic action

- Hormone Replacement may be tried in post menopausal women

Alternative Treatment Options

- Another management consideration is gastroespophageal testing, that may reveal acid reflux disease or esophageal motility disorders.
- Non-pharmacologic options for pain management:
  - Exercise training,
  - Transcendental meditation,
  - Cognitive behavioral therapy,
  - Transcutaneous electrical nerve stimulation(TENS),
  - Spinal cord stimulation

Algorithm to manage chest pain without obstructive CAD


Patient With Chest Pain
Symptoms Stable?
Yes
No
Myocardial Stress Evaluation (Gated-SPECT, MRI, or PET)*
Normal Myocardial Stress Evaluation?
Yes
No
Coronary Angiography
Evaluate Nonischemic Cardiac and Noncardiac Causes of Chest Pain
Consider Tricyclic Antidepressant Therapy
Cardiac Risk Factor Management
Normal Angiography or Nonobstructive CAD (<50% Luminal Diameter Stenosis)?
Yes
No
Consider Coronary Vascular Function Study
Medical Management
Consider Coronary Revascularization
Normal Coronary Vascular Function Study Results?
Yes
No
Aggressive Medical and Symptom Management (Aspirin, β-Blockers, Statins, Angiotensin-Converting Enzyme Inhibitors, Tricyclic Antidepressants, Exercise Training)

Conclusions

- A functional assessment of both the epicardial coronary arteries and the coronary microcirculation is necessary to diagnose MVA
- This is necessary to avoid misdiagnosing these patients with non cardiac chest pain
- Use of both classical and novel anti-anginal medications should be customized to individual patients


Happy Holi
Thank you for your kind attention
.....and best wishes !!!